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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/010,377	01/21/1998	S.A. RUBIN	015270-00430	8602

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/010,377	RUBIN ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18, 20-22* is/are pending in the application.

4a) Of the above claim(s) *21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 9/11/03 has been entered.

Claims 1-18 and 20-22 are pending.

Claim 19 has been canceled previously.

Claims 21-22 have been withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.

Claims 1-18 and 20 are under consideration in the instant application.

Applicant traverses the restriction to claims 21-22 that are drawn to agents comprising peptides and peptides derivatives, including peptides set forth in SEQ ID NOS: 3-5 in the claimed methods and that were not explicitly claimed in the original claims.

Applicant asserts that a search for the peptides that have the same binding affinity as the anti-VLA-4 / anti alpha-4 antibodies would not be overly burdensome.

Applicant's comments concerning the rejections under 35 USC 112, first paragraph, are acknowledged. It is noted that such rejections have been an attempt to advance prosecution of the instant application in order for applicant to obviate the rejections under 35 USC 112, first paragraph, written description and enablement with respect to the recitation of "agents" and to limit the claims to those "agents" supported by the application as filed. However, applicant has continued to argue support for "agents". The search for prior art has been limited to anti-VLA-4 / anti-alpha-4 antibodies in the claimed methods.

As previously noted , newly submitted claims 21-22 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Newly submitted claims 21-22 were drawn to agents comprising peptides and peptides derivatives, including peptides set forth in SEQ ID NOS: 3-5 in the claimed methods of treating viral encephalitis previously not claimed explicitly. Claims 21-22 are drawn to the use of agents which differ in structure and modes of actions from the anti-VLA-4 / anti-alpha-4 antibodies prosecuted in the instant application.

In addition, applicant is reminded that MPEP 803 states that the Inventions be either independent or distinct and a burden on the Examiner if restriction is required. Also, applicant's attention is directed to MPEP 806.05 for issues of distinctness.

Regarding applicant's comments about undue burden, the MPEP 803 states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search".

In contrast to applicant's reliance on the generic ability of agents that have binding affinity for VLA-4, applicant is reminded that antibodies and peptides do differ in physiochemical structures and modes of action to such an extent and require non-coextensive searches to such an extent that they are considered separately patentable. The examiner notes that these molecules do not share a substantial structural feature essential to a common utility

Applicant may consider submitting evidence or identifying such evidence now of record showing the anti-VLA-4 antibodies and specific peptides supported by the specification are obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

2. Applicant is reminded that the USSN is 09/**010**,377 and not 09/**101**,377 as indicated in the top right corner of applicant's Reply, filed 9/903.

3. Applicant's arguments, filed 9/11/03 are acknowledged.

Although the prior art of record is deemed appropriate still, the New Grounds of Rejection are considered to more directly address treating viral encephalitis with VLA-4-specific inhibitors including VLA-4-specific antibodies.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-8, 11, 14-18 (and non-elected claim 21) stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating viral encephalitis with "antibodies that bind the alpha-4 subunit of VLA-4" and peptides having the formula set forth in SEQ ID NOS: 3/4/5 as disclosed on pages-10 of the instant specification, does not reasonably provide enablement for any "agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin". The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 9/11/03, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments, filed 9/11/03 and the examiner's rebuttal are essentially the same of record.

Applicant asserts that the specification does teach how to find and screen various agents, including antibodies, peptides and small molecules, for the requisite ability to inhibit binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin.

As applicant has acknowledged, the specification provides for methods to test for other potential therapeutic agents for the appropriate binding specificity and/or the capacity to block the interaction of VLA-4 with inflamed endothelial cells, VCAM-1 expressing cells or purified VCAM-1.

Therefore, in providing a description on how to conduct screening assays, the specification essentially calls for the use of trial and error to attempt to find a compound that has the requisite ability to inhibit binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin. There is insufficient guidance in the way of selecting a particular compound or narrowing the range of candidates in order to find a suitable compound without the need of undue experimentation, other than "antibodies that bind the alpha-4 subunit of VLA-4" and peptides having the formula set forth in SEQ ID NOS: 3/4/5 as disclosed on pages-10 of the instant specification and known in the prior art. The instant application provides for assays for identifying agents which possess certain desired characteristics and identifies certain broad categories of agents that might work amounts to a starting pont or a direction for further research. The specification does not provide sufficient guidance or specificity as to execute the plan or invitation for the skilled artisan to experiment practicing the invention, encompassed by the scope of the claimed agents employed in the claimed methods.

Applicant has argued that pages 9-10 and 15 provides for agents that specifically inhibit VCAM-1 binding to the $\alpha 4$ subunit of VLA-4.

Again, as pointed out previously, the disclosure of particular peptides having the formula set forth in SEQ ID NOS: 3/4/5 as set forth on pages 9-10 of the instant specification; such peptides are considered enabled.

It is noted that these peptides are disclosed in WO 96/01644.

Again, applicant should recite these peptides in the claims.

In traversing the position that the peptides disclosed in WO 96/22966; WO 96/20216; WO 96/00581 and WO 9606108 do not need to be incorporated by reference, applicant has asserted that the reliance on the disclosure of other peptides disclosed in WO 96/22966; WO 96/20216; WO 96/00581 and WO 9606108 does not constitute essential subject matter. In addition to the reliance on the identification of certain agents disclosed in the specification, applicant submits that other reagents can be identified by various routine methods and well within the purview of the skilled artisan. Such assertions are not found convincing for the reasons of record and that set forth herein.

Also, applicant's comments have included the argument that the claims are drawn to methods and not directed to specific agents, which have not been found convincing in that the claimed methods rely upon specific agents in order to treat viral encephalitis. Similarly, applicant's submission that the identify of the agents are not essential materials does not comport with the ability to make and use agents to treat viral encephalitis, as encompassed by the claimed methods.

Again, applicant appears to rely upon the disclosure of other peptides disclosed in WO 96.22966; WO 96/20216; WO 96/00581 and WO 9606108 as well as U.S. Patent No. 5,510,332 (1449; #AB).

Here, it appears applicant is attempting to incorporate by reference essential subject matter to non-U.S. Patents.

In contrast to relying upon either SEQ ID NOS: 3/4/5 or U.S. Patent No. 5,510,332 which are disclosed in the instant specification as filed; applicant is attempting to incorporate by reference essential subject matter either to non-U.S. Patents or to material not disclosed in the application as filed.

A more thorough review of applicant's arguments and the examiner's rebuttal of record can be found in Paper No. 28.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of "any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin"or "that specifically bind the alpha-4 subunit of VLA-4", and still provide or maintain sufficient activity to treat viral encephalitis would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Again, applicant is invited to recite the particular peptides having the formula set forth in SEQ ID NOS: 3/4/5 as set forth on pages 9-10 of the instant specification into the claimed methods.

Otherwise, applicant's arguments have been fully considered but are not found convincing essentially for the reasons of record, as the claims read on any agent that inhibits binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin.

Applicant's arguments have not been found persuasive with the breadth of "agents that inhibit binding of leukocytes to brain endothelial cells via leukocyte surface antigen alpha-4 integrin.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-2, 4-8, 11, 16, 18 and 20 are rejected under 35 U.S.C. § 102(e) as being anticipated by Thorsett et al. (U.S. Patent No. 6,001,809) (see entire document) in further evidence of The Merck Manual of Diagnosis and Therapeutics, 16th Edition edited by Berkow et al., Merck Research Laboratories, Rahway, NJ, 1992, pages 1472-1474).

Thorsett et al. teach methods of treating viral encephalitis (e.g., see column 10, paragraph 2) with inhibitors of VLA-4, including selecting for oligopeptides that block VLA-4-mediated adhesion , wherein the oligopeptides are selected via sequence analysis with antibodies that inhibit VLA-4 binding to VCAM-1 (see entire document, including Description of the Preferred Embodiments, including column 5). The pharmaceutical compositions can be administered as prophylaxis or therapy in a patient already suffering from the disease or at least partially arrest the symptoms of the diseases or complications (column 10, paragraph 5). Amounts effective for use will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the inflammation, the age, weight and general condition of the patient (column 10, paragraph 5). Therefore, the prophylactic and therapeutic administration comprises monitoring the patient.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to inhibit or block cellular adhesion associated a number of disorders and diseases including viral meningitis and encephalitis. It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

The Merck Manual teach viral encephalitis is caused by arboviruses, polioviruses, echoviruses, coxsackieviruses, and herpes simplex (see pages 1472-1474). In addition, meningitis with no evidence of bacterial organisms is considered aseptic and caused by viral infections (see pages 1472-1474). Therefore, one of ordinary skill in the art would have immediately envisaged herpes virus or arbovirus as the source of viral infection of viral encephalitis at the time the invention was made.

It is acknowledged that the elected invention is drawn to using anti-VLA-4 / anti alpha-4 antibodies in the claimed methods. However, given the application of Thorsett et al. (U.S. Patent No. 6,001,809) in the obviousness rejection under 35 USC 103 below, Thorsett et al. is applied here in a rejection under 35 USC 102(e) since it anticipates the broad claims encompassing "agents".

10. Claims 1-18 and 20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Thorsett et al. (U.S. Patent No. 6,001,809) in view of The Merck Manual of Diagnosis and Therapeutics, 16th Edition edited by Berkow et al., Merck Research Laboratories, Rahway, NJ, 1992, pages 1472-1474) and Bendig et al. (U.S. Patent No. 5,840,299) AND/OR Yednock et al. (U.S. Patent No. 6,033,665).

Thorsett et al. teach methods of treating viral encephalitis (e.g., see column 10, paragraph 2) with inhibitors of VLA-4, including selecting for oligopeptides that block VLA-4-mediated adhesion , wherein the oligopeptides are selected via sequence analysis with antibodies that inhibit VLA-4 binding to VCAM-1 (see entire document, including Description of the Preferred Embodiments, including column 5).

Thorsett et al. also teach that the pharmaceutical compositions can be administered as prophylaxis or therapy in a patient already suffering from the disease or at least partially arrest the symptoms of the diseases or complications (column 10, paragraph 5).

Amounts effective for use will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the inflammation, the age, weight and general condition of the patient (column 10, paragraph 5). Although the primary reference differs from the claimed methods of monitoring the patients for encephalitis per se, the prior art teachings of prophylactic and therapeutic administration comprises monitoring the patient or would make obvious to monitor the condition of the treated patient to one of ordinary skill in the art at the time the invention was made. In addition, The Merck Manual teach Diagnosis of patients with viral encephalitis and aseptic meningitis (pages 1472-1475). Here, asymptomatic symptoms and signs known to one of ordinary skill at the time the invention was made are indicated (page 1473).

In addition, the Merck Manual teach the Etiology, Pathology, Diagnosis and Prognosis and Treatment of viral encephalitis and aseptic meningitis. The Merck Manual teach viral encephalitis is caused by arboviruses, polioviruses, echoviruses, coxsackieviruses, and herpes simplex (see pages 1472-1474). In addition, meningitis with no evidence of bacterial organisms is considered aseptic and caused by viral infections (see pages 1472-1474). Therefore, one of ordinary skill in the art would have immediately envisaged herpes virus or arbovirus as the source of viral infection of viral encephalitis at the time the invention was made.

Although Thorsett et al. teach the use of anti-VLA-4 / anti-α4 antibodies in screening for inhibitory VLA-4-specific oligopeptides, Thorsett et al. differs from the claimed methods by explicitly teaching that anti-VLA-4 / anti-α4 as the inhibitory VLA-4-specific agent.

Bendig et al. teach using inhibitory VLA-4α-specific antibodies, including humanized antibodies and the 21.6 specificity to treat encephalitis (see entire document, including VII. Methods of Treatment on columns 14-16). Therefore, the anti-VLA-4 / anti-α4 antibody specificities as well as antibody forms and compositions encompassed by the claims (e.g. claims, 8-13 and 20).

Yednock teaches the using inhibitory VLA-4α-specific antibodies, including humanized antibodies and the 21.6 specificity to treat brain inflammation, including meningitis (see entire document, including Detailed Description of the Invention and Claims). Therefore, the anti-VLA-4 / anti-α4 antibody specificities as well as antibody forms and compositions encompassed by the claims (e.g. claims, 8-13 and 20).

Although the primary reference differs from the claimed methods pediatric nature of the patients or providing antiviral/anti-inflammatory agents in addition per se, it would have been obvious to one of ordinary skill at the time to provide all patients in need, including pediatric patients with inhibitory VLA-4α-specific antibodies to inhibit viral encephalitis and to provide said VLA-4α-specific antibodies in combination with other current or standard therapeutic regimens such as antiviral or anti-inflammatory agents in order to target the virus or its effects in order to treat viral encephalitis.

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Bendig et al. AND/OR Yednock to those of Thorsett et al. to substitute inhibitory VLA-4α-specific antibodies in the treatment of viral encephalitis, given the same properties of the referenced VLA-4α-specific antibodies and VLA-4α-specific peptides and the same therapeutic endpoints of inhibiting inflammatory responses, including in the brain. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

After January 20, 2004, Phillip Gambel's telephone number will be (571) 272-0844 and Christina Chan's telephone Number will be (571) 272-0841.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306

PHILLIP GAMBEL

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